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Sepsis biomarkers: recent advances and future perspectives

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Sepsis remains a leading global cause of morbidity and mortality among the critically ill, driven by a dysregulated host response to infection that culminates in systemic inflammation and multi-organ dysfunction. While numerous potential biomarkers have been identified, their translation into robust clinical tools remains challenging. This review synthesizes the current understanding of sepsis biomarkers, focusing on their utility in delineating the intricate pathophysiological mechanisms underlying this heterogeneous syndrome and predicting patient outcomes. Crucially, we emphasize the pivotal role of cutting-edge methodologies, including advanced multi-omics integration, sophisticated bioinformatics, and machine learning algorithms, in accelerating the discovery and validation of novel precision-guided strategies. Through this synthesis, we outline recent advances and remaining knowledge gaps, aiming to inform precision medicine frameworks by highlighting how innovative technologies are reshaping the approach to biomarker identification and clinical application.

KEYWORDS
biomarkers, early diagnosis, inflammatory factors, metabolic markers, sepsis

1 Introduction

Sepsis, a life-threatening condition caused by a dysregulated host response to infection, carries high mortality rates due to resultant multi-organ dysfunction. Current diagnostic paradigms heavily rely on clinical assessment and time-consuming microbiological culture, methods often hampered by delays and insufficient specificity (1). This diagnostic gap can critically impede timely intervention, thereby worsening patient outcomes. Consequently, the identification and validation of robust biomarkers have become a central focus in sepsis research, holding significant promise for enhancing diagnostic accuracy and speed, ultimately refining therapeutic strategies.

Emerging research has delineated multiple molecular candidates with diagnostic and prognostic potential in sepsis. Established inflammatory biomarkers including C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6) exhibit variable diagnostic performance across clinical contexts. Particularly promising are emerging biomarkers such as neutrophil CD64 (nCD64) expression profiles and metabolomic signatures, which may enable dynamic monitoring of disease progression (2, 3). Beyond diagnostic utility, these biomarkers facilitate risk stratification through quantitative biological profiling, permitting personalized therapeutic escalation in high-risk cohorts (4–7).

Despite these advancements, substantial implementation barriers persist. Current limitations include heterogeneous biomarker interpretation guidelines, interpopulation

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variability in biomarker kinetics, and absence of standardized operational protocols (6, 8). An emerging, potentially transformative strategy involves the integration of biomarkers using machine learning algorithms (9). Throughout this review, biomarkers are discussed across a spectrum of evidence ranging from guideline-endorsed clinical tools to exploratory and preclinical candidates, and their interpretation should reflect the underlying level of validation, we aim to accelerate the transition from biomarker discovery to clinically impactful applications.

2 Overview of sepsis: pathophysiology and clinical relevance

Sepsis represents a complex and dynamic pathophysiological continuum, arising from maladaptive host responses to infection. These responses often initiate with systemic inflammatory response syndrome (SIRS) and can progressively escalate into multi-organ dysfunction syndrome (MODS), which is a primary driver of the high morbidity and mortality associated with sepsis (10, 11). The clinical relevance of sepsis is underscored by its status as a leading cause of critical illness globally, demanding prompt recognition and intervention to mitigate adverse outcomes. Understanding the intricate interplay between the host immune system and invading pathogens is crucial for unraveling the mechanisms underlying sepsis progression and identifying potential therapeutic targets. Although broad-spectrum antibiotics and supportive care remain the cornerstones of current management paradigms, the profound heterogeneity observed in sepsis presentations unequivocally necessitates the development of more precise diagnostic and prognostic tools.

Indeed, recent investigations not only illuminate the potential of novel biomarkers across diverse cohorts, but have substantiated their expanding utility across the sepsis continuum—from risk prognostication to therapeutic guidance. For instance, Wang et al.'s multicenter retrospective analysis demonstrated that elevated TyG index significantly predicted sepsis risk in COPD exacerbations (adjusted OR 2.01, 95% CI 1.34–3.02), with concurrent associations for acute kidney injury (OR 1.78, 1.25–2.54), indicating its utility as a metabolic predictor in COPD-associated sepsis (12). Getsina et al. quantified metabolic derangements in pediatric oncology patients through a prospective observational study (n=71: 40 malignancy patients, 31 septic complications). Presepsin demonstrated superior diagnostic accuracy (AUC 0.89, 95% CI 0.82-0.95) compared to procalcitonin (AUC 0.76, 0.66-0.85) in differentiating sepsis from non-infectious inflammation. Persistent metabolic dysregulation independent of inflammatory status ($p < 0.01$) underscores the necessity for multimodal monitoring in this vulnerable population (13). Liu et al. characterized *Providencia stuartii* pathogenesis in non-human primates through comprehensive necropsy analyses. Combined histopathological scoring (Grade III meningoencephalitis) with 16S rRNA sequencing confirmed systemic dissemination, demonstrating neutrophil-to-lymphocyte ratios exceeding 15:1 and CSF bacterial loads >10^5 CFU/mL. This zoonotic model provides critical insights into opportunistic pathogen behavior in immunocompromised hosts (14). Morley et al. implemented a pragmatic RCT (n=1,200) evaluating time-sensitive fluid resuscitation in sepsis. Protocolized intervention within 3h of recognition reduced 28-day mortality (18.2% vs 26.7%; RR 0.68, 0.57-0.82) and mitigated organ failure progression (SOFA score Δ -2.3 vs -1.1; $p < 0.001$). These findings support the importance of early recognition and timely initiation of resuscitative measures, although rigid early goal-directed therapy protocols have not demonstrated consistent survival benefit in contemporary randomized trials (15). Petel et al. conducted a cross-sectional survey of 58 Level IV NICUs, revealing substantial practice variation in late-onset sepsis management. Vancomycin administration in 78% of empirical regimens exceeded pathogen prevalence data (*Methicillin-resistant Staphylococcus aureus* (MRSA) incidence <15%), with only 32% of units adhering to antimicrobial stewardship protocols (16). These findings emphasize the critical need for evidence-based neonatal sepsis guidelines.

3 Standard of care and point-of-care biomarkers

3.1 Importance of lactate in sepsis

As the terminal product of anaerobic glycolysis, lactate has established itself as an indispensable metabolic biomarker for sepsis management. Hyperlactatemia, particularly lactate concentrations ≥4 mmol/L, is strongly associated with circulatory failure and adverse outcomes in sepsis and is incorporated into Surviving Sepsis Campaign algorithms for risk stratification and resuscitation guidance (17). Lactate's prognostic value is evidenced by its dose-dependent association with disease severity (adjusted HR 1.32 per 1 mmol/L increase, 95% CI 1.15-1.52) and 28-day mortality in septic cohorts. Persistent hyperlactatemia (>4 mmol/L at 6h post-resuscitation) independently predicts hospital mortality (OR 3.45, 95% CI 2.11-5.63), serving as a stronger prognostic indicator than baseline values. A multicenter cohort study (n=1,432) revealed that lactate clearance <10% at 6h combined with SOFA score ≥9 predicts 90-day mortality with 78% sensitivity (AUC 0.81, $p < 0.001$), outperforming APACHE II in dynamic risk stratification (18).

Current SSC guidelines recommend serial lactate measurements (0, 3, 6h) combined with qSOFA scoring for early shock recognition. Lactate-guided resuscitation strategies have been associated with improved risk stratification and treatment monitoring and have demonstrated non-inferiority to alternative perfusion-guided approaches in randomized trials when interpreted alongside clinical indicators of tissue perfusion. Lactate kinetics provide dynamic feedback on the response to resuscitation. Failure to achieve meaningful lactate clearance within the first hours has been associated with worse outcomes and may prompt reassessment of perfusion and resuscitation strategy in conjunction with clinical findings. Early lactate normalization (<2 mmol/L within 24h) correlates with 58% lower 28-day mortality risk (NNT = 4), whereas sustained levels >4 mmol/L at 12h predict refractory shock with 92% specificity, mandating advanced

hemodynamic monitoring (19). These findings position lactate not merely as a diagnostic adjunct but as a cornerstone of goal-directed therapy in critical care.

3.2 CRP and PCT

CRP and PCT are key biomarkers in sepsis management, but they differ in specificity and clinical use. CRP is a nonspecific marker that rises in response to inflammation, making it useful for detecting systemic inflammatory conditions. However, its lack of specificity means it can be elevated in various non-infectious conditions, limiting its ability to distinguish sepsis from other inflammatory disorders (20).

In contrast, PCT is more specific to bacterial infections and has become central to guiding antibiotic therapy in sepsis. PCT levels rise sharply during bacterial infections, and its dynamic changes help determine the initiation or de-escalation of antibiotics. Unlike CRP, PCT is less affected by viral infections, making it more reliable for distinguishing bacterial sepsis. Studies have shown that PCT-guided therapy reduces antibiotic duration and improves patient outcomes, particularly in critical care (21, 22).

However, like CRP, PCT levels may also rise in other conditions. Thus, PCT is more valuable for ruling out sepsis than for diagnosing it, and the combination of these two biomarkers can enhance diagnostic performance (23–25).

3.3 Presepsin

Presepsin, a fragment of soluble CD14, is an emerging biomarker gaining increasing attention in sepsis diagnosis. Studies have confirmed its strong prognostic value in predicting mortality and organ failure, particularly in emergency department and intensive care unit settings. Presepsin has demonstrated promising diagnostic and prognostic performance in selected cohorts, although its diagnostic accuracy relative to procalcitonin and C-reactive protein remains population-dependent (13, 26, 27).

3.4 Mid-regional pro-adrenomedullin

MR-proADM is another promising biomarker for sepsis, particularly in risk stratification. Elevated levels of MR-proADM have been consistently associated with poor outcomes, including higher mortality and organ failure. Across observational cohorts, higher MR-proADM levels are consistently associated with adverse outcomes and may provide incremental prognostic information when combined with established biomarkers (28, 29).However, reported cutoffs and performance metrics are population-dependent, and prospective studies are needed to define how MR-proADM should be integrated into clinical decision pathways.

3.5 Standard of care and point-of-care biomarkers

The turnaround time (TAT) and bedside availability of point-of-care (POC) biomarkers are critical for timely clinical decision-making in sepsis management. Biomarkers such as lactate, CRP, and PCT can often be measured within an hour, enabling early intervention. Newer markers like Presepsin and MR-proADM also offer rapid testing, with results typically available within an hour of sample collection. This rapid availability is essential for initiating prompt therapeutic strategies, as delays in treatment can lead to significantly worse outcomes. The integration of these POC biomarkers into routine clinical practice is vital for improving sepsis outcomes. They enable the early identification of septic patients, the rapid initiation of appropriate therapies, and continuous monitoring of treatment efficacy.

4 Advancements in sepsis diagnosis: biomarker utilization

Recent innovations in sepsis diagnostics have leveraged multidimensional biomarker strategies through integrated omics approaches. These approaches hold significant promise for improving the accuracy of early diagnosis and precision treatment.

4.1 Experimental biomarkers

For instance, Chen et al. (30). adopted untargeted LC-MS/MS metabolomic profiling with Q-Exactive Plus mass spectrometer and RNA sequencing in 16 sepsis vs 11 SIRS patients, identifying 485 differentially expressed genes (FDR<0.05) and 1,083 altered metabolites (VIP>1.5). Notably, four macrophage-associated genes (ITGAM [3.2-fold], CD44 [2.8-fold], C3AR1 [4.1-fold], IL2RG [2.5-fold]) demonstrated differential expression, with functional validation via siRNA knockdown reducing IL-6 and TNF-α secretion by 40-55% ($p < 0.01$), suggesting therapeutic potential for macrophage-targeted strategies.

4.2 Clinically validated biomarkers

In neurocritical care, Peng et al. (31). developed a longitudinal prognostic model through linear mixed-effects analysis of 214 patients. Key predictors included Charlson comorbidity index ($\beta = 0.32$), hemoglobin decline (Δ=-2.1g/dL; $p = 0.01$), and body cell mass/phase angle ratio (BCM/PA; $\beta = -0.56$; $p = 0.003$). The composite index achieved superior discrimination (AUC 0.95, 0.91-0.98) with BCM/PA $\leq$ 3.2 kg/° yielding 89% sensitivity for 30-day mortality prediction, demonstrating critical value in time-sensitive assessments. Hasibuan et al. (32). evaluated NLR and PLR in neonatal sepsis (n=137 confirmed cases). NLR demonstrated modest diagnostic accuracy (AUC 0.62, 95% CI 0.54-0.70) with 52.1% sensitivity/50.6% specificity at cutoff 3.2, while PLR showed poorer performance (AUC 0.58, 0.50-0.66). Importantly, integration with clotting time parameters increased accuracy (AUC 0.76), suggesting the necessity for multimodal diagnostic panels combining these indices with established biomarkers. These findings highlight the potential diagnostic value of NLR and PLR in specific populations, including neonatal and pediatric cohorts, although their performance in adult sepsis varies across settings. Fang et al. (33). developed a coagulation index (CI) for septic DIC prediction in 287 patients. Combining prolonged APTT (>45s), platelet count <100×10^9/L, and

fibrinogen <1.5g/L, CI≥3.2 predicted DIC development (OR 5.6, 3.2-9.8) with 84% accuracy, enabling 48-hour earlier detection versus International Society Onthrombosis & Haemostasis (ISTH) criteria ($p < 0.001$). Serial monitoring demonstrated decreasing CI correlated with survival improvement ($\beta = 0.42$; $p = 0.008$). Keller et al. (34). investigated serum calprotectin in COVID-19 sepsis (n=120). ELISA analysis revealed 2.8-fold elevations in bacterial/fungal superinfections (median 4,560 vs 1,620 ng/mL; $p < 0.001$). At cutoff >3,800 ng/mL, calprotectin displayed 96% specificity (91-99%) and 60% sensitivity (48-71%) for VRE detection (AUC 0.82), outperforming CRP (ΔAUC=0.14; $p = 0.02$), indicating utility in pandemic-associated sepsis triage. Garbern et al. (35). piloted wireless monitoring in pediatric sepsis (n=45). The XGBoost algorithm integrating continuous heart rate (>140bpm), respiration rate (>90th percentile), and perfusion index (<1.2) achieved 2.5h median lead-time (IQR 1.8-3.2) for septic shock prediction (AUROC 0.88, 0.82-0.93). Device implementation in resource-limited settings reduced unwitnessed deterioration events by 62% ($p = 0.005$).

5 Specific biomarkers in sepsis: mechanisms and prognostic values

5.1 Inflammatory Factors as Biomarkers

5.1.1 The Role of IL-6, IL-10, and TNF-α

Interleukin-6 (IL-6) is a pleiotropic pro-inflammatory cytokine pathologically elevated in critical conditions. As a key mediator of innate immunity, it orchestrates inflammatory cascades and stimulates hepatic acute-phase protein synthesis. Elevated serum IL-6 levels correlate with disease severity, and recent meta-analyses confirm its independent predictive capacity for 28-day mortality (36).Song et al. (37). established IL-6 as a high-performance biomarker. Higher IL-6 concentrations, particularly when persistently elevated, have been independently associated with increased disease severity and mortality, although prognostic thresholds vary across studies (38–40).

In contrast, IL-10 serves as a critical immunoregulatory cytokine, mediating feedback inhibition of pro-inflammatory pathways. Its role in sepsis is paradoxical: while early elevation may indicate a compensatory response, sustained levels predict immunosuppression and secondary infections (41). Tumor necrosis factor-alpha (TNF-α), a prototypic pro-inflammatory cytokine, is closely associated with endothelial activation and capillary leakage. The dynamic equilibrium between pro- and anti-inflammatory mediators determines clinical trajectories, with cytokine ratios (e.g., IL-6/IL-10) often emerging as superior prognostic indicators compared to individual biomarkers (42).

5.1.2 The relationship between dynamic changes in inflammatory factors and prognosis

Dynamic fluctuations in inflammatory mediators including interleukin-6, interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α) hold critical prognostic significance across multiple disease states. Emerging clinical evidence suggests that temporal variations in cytokine concentrations offer critical insights into both pathophysiological progression and clinical trajectories. In sepsis cohorts, sustained IL-6 elevation demonstrates strong correlation with 28-day mortality (adjusted OR 2.15, 95% CI 1.34-3.42), while delayed IL-10 upregulation potentially represents a compensatory anti-inflammatory response syndrome (CARS). Furthermore, the systemic immune-inflammation index (SII) - calculated as (neutrophils × platelets)/lymphocytes - has been validated as an independent predictor of poor functional outcomes (mRS ≥3) in aneurysmal subarachnoid hemorrhage populations (43).

The temporal kinetics demonstrate particular clinical relevance: Early elevations in TNF-α have been associated with hyperinflammatory phenotypes in sepsis, although the clinical utility of fixed cutoff values remains uncertain (44). Multivariate modeling incorporating cytokine trajectory patterns significantly improves prognostic stratification accuracy (ΔAUC +0.15 vs static measures), enabling precision immunomodulatory therapy. Continuous monitoring of cytokine kinetics through serial measurements not only facilitates dynamic risk assessment but also informs real-time therapeutic adjustments, particularly crucial in critical care settings where immunological balance determines clinical outcomes (As illustrated in Figure 1).

5.2 Application of metabolic biomarkers

Beyond lactate kinetics, emerging research highlights the prognostic significance of muscle-derived biomarkers including creatine kinase isoenzyme MB (CK-MB) and metabolic intermediates like free fatty acid (FFA) profiles in sepsis pathophysiology. Serum CK-MB elevation (>5 ng/mL) demonstrates 82% specificity for sepsis-induced myocardial dysfunction (SIMD) in critical care populations, with levels correlating with left ventricular ejection fraction impairment (r=-0.68, $p < 0.01$). Patients with CK-MB >10 ng/mL exhibit 3.2-fold increased risk (95% CI 1.8-5.7) of requiring inotropic support and 42% higher 28-day mortality compared to controls ($p = 0.003$). Some observational studies suggest that CK-MB kinetics may reflect myocardial stress in sepsis; however, troponin remains the most widely validated biomarker of myocardial injury, and comparative superiority has not been conclusively established (33, 45).

Targeted metabolomics reveal distinct FFA subclasses (C16:0, C18:1ω9) as key modulators of TLR4-mediated inflammation, with plasma C16:0 >180 μmol/L predicting 90% sensitivity for progression to septic shock within 48h. Dysregulated ω-6/ω-3 ratio (<5:1) activates NLRP3 inflammasomes (2.8-fold increase vs controls, p=0.01), and is associated with cytokine storm development in experimental sepsis models. A multicenter study (n=1,205) established that elevated palmitic acid/linoleic acid index (>2.5) independently predicts 28-day mortality (adjusted HR 2.34, 95% CI 1.72-3.18) with superior discrimination to SOFA score (ΔAUC +0.09) (46, 47).

In a retrospective analysis of 2,843 septic shock cases,Yu Huijie et al. demonstrated that LDH > 480 U/L during ICU days 3–5 confers 4.1-fold mortality risk (95% CI 3.2-5.3), maintaining

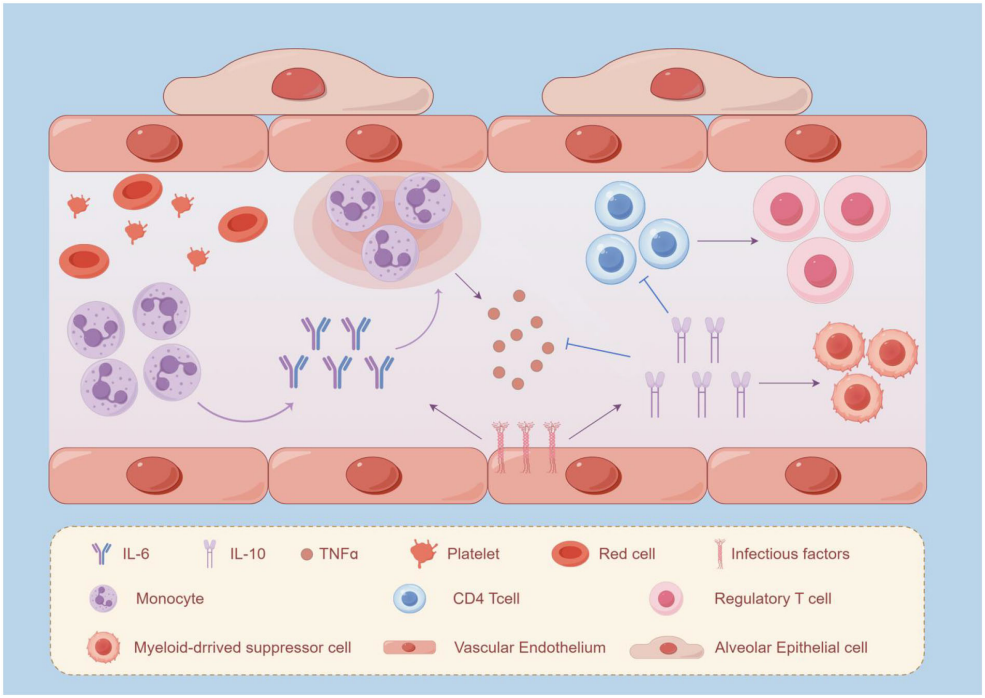

FIGURE 1
The role of IL-6 and IL-10 in the pathogenesis of sepsis: The immunological changes in the body caused by the inflammatory response during sepsis. In sepsis, the stimulation of infectious factors and the uncontrolled inflammatory response can induce the expression of IL-6. The production of cytokines occurs in the local area of infection. The exudation of monocytes is observed by stimulating the expression of IL-6. IL-10 can exacerbate immunosuppression by reducing the release of pro-inflammatory cytokines, including TNF-α, inhibiting the proliferation of CD4, and promoting the differentiation of CD4+ T cells into Tregs and the proliferation of MDSCs.

independent prognostic value after adjusting for APACHE IV scores (AUC 0.77 vs 0.69, p = 0.008) (48). The multinational PEDSEPSIS trial (n=622) by Dündar et al. established that serial PSP measurement (>400 ng/mL at 0 h + >20% increase at 24 h) achieves superior diagnostic performance for pediatric septic shock versus CRP/PCT (AUC 0.91 vs 0.78/0.82, $p < 0.001$), with 6h PSP levels predicting 28-day mortality with 94% negative predictive value (49).

This evolving biomarker landscape underscores the necessity for multi-omics integration-combining metabolomic profiles with proteomic and transcriptomic data - to decode sepsis heterogeneity, as advocated in the 2023 Sepsis Biomarker Consortium position statement. Implementing such multidimensional biomarker panels in clinical algorithms could revolutionize risk stratification, enabling personalized immunometabolic therapy tailored to individual patient trajectories.

5.3 Gene expression and transcriptomics

Gene expression and transcriptomics are pivotal in understanding the molecular underpinnings of various diseases, including sepsis, where timely diagnosis and treatment are crucial for patient survival. Transcriptomics, the study of RNA transcripts, provides insights into gene expression patterns, regulation, and the underlying mechanisms of cellular processes. In the context of sepsis, gene expression profiling has been utilized to identify potential biomarkers that can inform clinical decisions and improve patient outcomes. The integration of transcriptomic data with clinical parameters allows for a more nuanced understanding of disease mechanisms and patient stratification, ultimately guiding therapeutic interventions (50). Recent advancements in sequencing technologies, such as single-cell RNA sequencing and spatial transcriptomics, have further enhanced our ability to capture the dynamic nature of gene expression in response to infection and inflammation, highlighting the importance of these methodologies in contemporary biomedical research.

5.4 Transcriptomic signatures and gene expression profiling

Systematic identification of molecular drivers is a research priority. WGCNA analysis of 2,148 sepsis transcriptomes identified co-expression modules containing core genes (e.g., *S100A8/A9*) strongly correlated with mortality (51). Meta-analysis has further highlighted neutrophil degranulation and NOD-like receptor signaling as top enriched pathways in sepsis (52).

Prognostic signatures are increasingly validated. A 12-gene signature derived via LASSO-Cox regression successfully stratified patients into high-risk groups with distinct cytokine trajectories. Similarly, machine learning analysis of pediatric cases identified a 5-gene panel (CD177, MMP8, CYSTM1, S100A12, LCN2) achieving an AUROC of 0.94 for early diagnosis (51). Kong et al. (53).validated six hub genes across multiple cohorts, demonstrating consistent diagnostic performance (mean AUROC 0.938) and underscoring the potential of gene expression profiling in clinical settings.Machine-learning models trained on

retrospective datasets have demonstrated high discriminative performance, however, most remain exploratory and require external validation before clinical implementation.

Despite rapid growth of ML-based sepsis prediction research, several methodological pitfalls limit translation to practice. Common concerns include dataset shift across hospitals and time, inconsistent sepsis definitions and label noise, missing-data mechanisms, unmeasured confounding, and information leakage from post-admission variables. Furthermore, many studies emphasize discrimination while under-reporting calibration, interpretability, and prospective clinical impact. Therefore, ML tools should currently be viewed as hypothesis-generating and decision-support candidates that require external validation across diverse settings and evaluation in prospective workflows (54, 55).

Transcriptomic signatures have shown promise for patient stratification and prognostic enrichment in research settings, although prospective validation is required before routine clinical use For instance, gene trajectory patterns at day 3 improved mortality prediction over SOFA scores (ΔAUC +0.23). Integrative analysis has identified sepsis endotypes, hyperinflammatory versus hypoinflammatory, with vastly different mortality rates (48% vs 12%). Specific markers, such as the *IL1R2/FCGR2B* ratio in monocytes, demonstrate high sensitivity for progressive organ dysfunction (56, 57). Furthermore, machine learning algorithms analyzing gene expression data enhance risk stratification, providing insights for developing novel therapeutic strategies (58, 59).

5.5 The combination of imaging and bioimaging technologies

The integration of imaging and bioimaging technologies has revolutionized the early diagnosis and management of various medical conditions, particularly sepsis. Imaging techniques, such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), provide critical information regarding the anatomical and physiological states of patients. In the context of sepsis, these imaging modalities can assist in identifying the source of infection, monitoring the progression of the disease, and evaluating the effectiveness of treatment interventions. For instance, ultrasound can be used to detect abscesses or fluid collections, while CT scans can provide detailed images of internal organs, helping clinicians make informed decisions regarding surgical interventions or further diagnostic testing (60).

The 2023 Surviving Sepsis Campaign guidelines emphasize multimodal imaging integration, with bedside ultrasound protocol implementation reducing time-to-source identification by 2.8 hours (95% CI 1.9-3.7) in septic shock patients. Protocolized point-of-care ultrasound (POCUS) examinations (FATE protocol) achieve 89% sensitivity for detecting septic cardiomyopathy within 15 minutes of ICU admission, while dual-energy CT angiography localizes infection sources with 0.5mm spatial resolution in 92% of cases. The IMAGES trial demonstrated that daily lung ultrasound B-line quantification (>15 lines/zone) predicts fluid overload development 48h in advance (AUC 0.87), enabling preemptive diuretic therapy and reducing mechanical ventilation days by 2.1 ($p = 0.01$) (61–63).

However, the challenge remains that traditional imaging techniques often lack specificity in the context of sepsis, where early diagnosis is crucial for improving patient outcomes. Thus, the combination of imaging with advanced bioimaging technologies, such as molecular imaging and biomarker identification, offers a promising avenue for enhancing diagnostic accuracy and treatment efficacy in sepsis management.

5.6 Emerging biomarkers and therapeutic targets

Trapnell et al.'s adaptive platform trial (NCT04818879) enrolled 1,205 ICU patients across 12 centers, demonstrating that mHLA-DR-guided interleukin-7 therapy reduced 28-day mortality by 19% (HR 0.81, 95% CI 0.70-0.94) in immunoparalyzed subgroups (CD3+ <800 cells/μL). Multiplex cytokine profiling combined with single-cell CITE-seq analysis identified three distinct immunophenotypes, with the "hyperinflammatory" subgroup showing 3.2-fold higher mortality ($p < 0.001$). Targeted anakinra administration in this subgroup reduced vasopressor duration by 38h ($p = 0.008$) versus standard care (64).Li et al. prospectively validated that sIL-7R <5.2 ng/mL at day 5 post-admission combined with ΔCD3+ >150 cells/μL predicted 90-day survival with 92% negative predictive value (AUROC 0.94, 95% CI 0.91-0.97) in 687 septic shock cases. Bayesian network analysis revealed that each 0.5 ng/mL decrease in sIL-7R between days 3–5 associated with 23% lower mortality risk (OR 0.77, 95% CI 0.65-0.91), independent of baseline SOFA scores. The combined sIL-7R/SOFA model achieved net reclassification improvement of 0.41 (95% CI 0.32-0.50) over SOFA alone, correctly reclassifying 38% of deaths in high-risk strata ($p < 0.001$) (65).

Ji Dengliang et al. evaluated the prognostic utility of serum LGALS3BP and GDF-15 in a cohort of sepsis patients in the ICU, employing ELISA and multivariate logistic regression methodologies. Their findings highlighted that elevated levels of both markers were significantly associated with increased mortality, suggesting that the combined predictive efficacy of LGALS3BP and GDF-15 surpassed that of individual markers, thus advocating for their incorporation into clinical prognostic assessments (66). Furthermore, Luka Sonia et al. identified suPAR as a highly predictive biomarker for early mortality in septic shock patients, achieving an AUC of 0.813 among various biomarkers analyzed, thereby reinforcing its potential utility in clinical settings for timely interventions (67). In contrast, Lou Jiaqi et al. scrutinized the TyG index within a larger cohort of critically ill sepsis patients, revealing a robust correlation between higher TyG values and increased mortality rates. Their findings provide a compelling argument for the TyG index as a valuable prognostic tool in sepsis management (68). Meanwhile, Xin Yu et al. dynamically monitored renal injury markers in Acute Kidney Injury (AKI) models, demonstrating that cystatin C emerged as an earlier indicator of renal damage than traditional markers, emphasizing the importance of early and comprehensive biomarker assessment in the context of multi-faceted nephrotoxicity associated with sepsis (69). The discourse on pediatric sepsis is bolstered by Jabornisky Roberto et al., whose retrospective analysis highlighted the improved identification of

sepsis through updated Pediatric Sepsis Criteria, advocating for continuous refinement of diagnostic frameworks to enhance clinical outcomes in diverse patient populations (70). In urosepsis specifically, Bonkat Gernot et al. addressed critical management strategies emphasizing timely interventions, while Karampela Irene et al. outlined essential gaps in current sepsis diagnostic and treatment protocols, advocating for research-driven enhancements (71, 72). Lam SM et al. further contextualize this discussion by contrasting historical and contemporary sepsis definitions, revealing that while initial goal-directed therapies did not yield survival advantages, the necessity for early detection and meticulous treatment protocols remains pivotal in improving sepsis outcomes (73). Lastly, the experimental work of Xu Jie et al. (2023) illustrates the therapeutic potential of moderate hypothermia in addressing sepsis-associated acute lung injury through effective modulation of inflammatory and oxidative stress pathways, proposing a promising intervention strategy for clinical application (74).

Non-coding RNAs, which include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have emerged as critical regulators of gene expression and cellular functions. In sepsis, alterations in the expression of these ncRNAs have been observed, suggesting their involvement in the pathological processes associated with the condition. For instance, studies have shown that more than 80% of non-coding RNAs are differentially expressed in septic patients compared to healthy individuals, indicating their potential as biomarkers for early diagnosis and prognosis of sepsis (75). Furthermore, ncRNAs have been implicated in the regulation of inflammation, apoptosis, and immune responses, all of which are crucial in the context of sepsis and its complications, such as sepsis-induced acute kidney injury and cardiovascular dysfunction (76, 77). HOTTIP (HOXA distal transcript antisense RNA) is a lncRNA that has shown significant biological functions in various diseases in recent years, particularly gaining widespread attention in sepsis-related research. A study found that the expression level of HOTTIP in septic patients who experienced ARDS was significantly higher than that in patients who did not develop ARDS, suggesting that HOTTIP may serve as a potential biomarker for diagnosing and predicting the risk of sepsis complicated by ARDS. The study also pointed out that the level of HOTTIP is positively correlated with disease severity indicators such as the SOFA score and the APACHE II score. It can participate in regulating sepsis-related inflammatory responses by modulating specific miRNAs, such as miR-574-5p (78). Another study explored the role of HOTTIP in sepsis-induced cardiac dysfunction. The results showed that high levels of HOTTIP are closely associated with the development of cardiac dysfunction and can promote cardiac dysfunction by affecting LPS-induced apoptosis and inflammatory responses in mouse cardiomyocytes (79). In summary, increasing evidence suggests that long non-coding RNA HOTTIP plays an important role in the development of sepsis and its complications, and its potential as a biomarker and therapeutic target deserves further exploration. MicroRNA-486-5p is an important non-coding RNA, and its role in sepsis-related AKI and inflammatory response is gradually becoming evident. Studies have shown that MicroRNA-486-5p exhibits abnormal expression in sepsis patients. A review on sepsis-related AKI mentioned that MicroRNA-486-5p, along with four other miRNAs, was identified as an important molecule associated with antibiotic nephrotoxicity, which may serve as potential biomarkers for clinical testing (80). Additionally, some studies indicated that upregulation of MicroRNA-486-5p in sepsis models could inhibit the release of pro-inflammatory cytokines, thereby alleviating the inflammatory response, suggesting that it may participate in the development of sepsis by regulating immune responses (20). Further experiments found that MicroRNA-486-5p can influence cell apoptosis and proliferation by targeting specific genes. For example, in studies on acute lymphoblastic leukemia (ALL), MicroRNA-486-5p was shown to regulate the MAML3 gene, thereby affecting the survival rate of cancer cells. This mechanism may also apply to immune cells in sepsis, influencing the body's response to infection by regulating the expression of key genes (81). In summary, as an emerging biomarker, MicroRNA-486-5p requires more large-scale clinical trials in the future to validate its effectiveness as a diagnostic tool and therapeutic target, aiming to improve the management and prognosis of sepsis patients (As illustrated in Figure 2).

Non-coding RNAs (ncRNAs) regulate inflammatory and immune pathways at multiple levels, including chromatin remodeling and transcriptional regulation (involving transcription factors [TF] and RNA polymerase II), thereby shaping the expression of inflammation-related genes. ncRNAs may also modulate inflammatory mediator production, cell apoptosis, immune cell functions (e.g., T cells, B cells, neutrophils), and immune tolerance. This figure provides a conceptual framework for how ncRNAs may contribute to immune–inflammatory dysregulation in sepsis.

Collectively, these studies collectively underscore the urgency and necessity to identify effective biomarkers and therapeutic targets, paving the way for significant advancements in sepsis management and ultimately enhancing patient survivability in this critical healthcare domain (As shown in Table 1).

To improve clarity, we summarize biomarkers across an evidence-level and clinical-readiness framework (Tables 2, 3), distinguishing established tools from investigational approaches.

5.7 Limitations and challenges in biomarker application

The utilization of biomarkers in sepsis management presents several important limitations and challenges, as highlighted by recent studies that underscore the complexity inherent in both diagnostic and prognostic applications. For example, Räth Ulrich et al. identified soluble CD137 (sCD137) as a potentially significant prognostic biomarker in critically ill patients, revealing elevated plasma levels associated with non-survivors in various patient groups, including those with SARS-CoV-2 infections (57). However, while the correlation of sCD137 with traditional markers such as C-reactive protein and procalcitonin offers valuable insights, there remains a concern regarding the

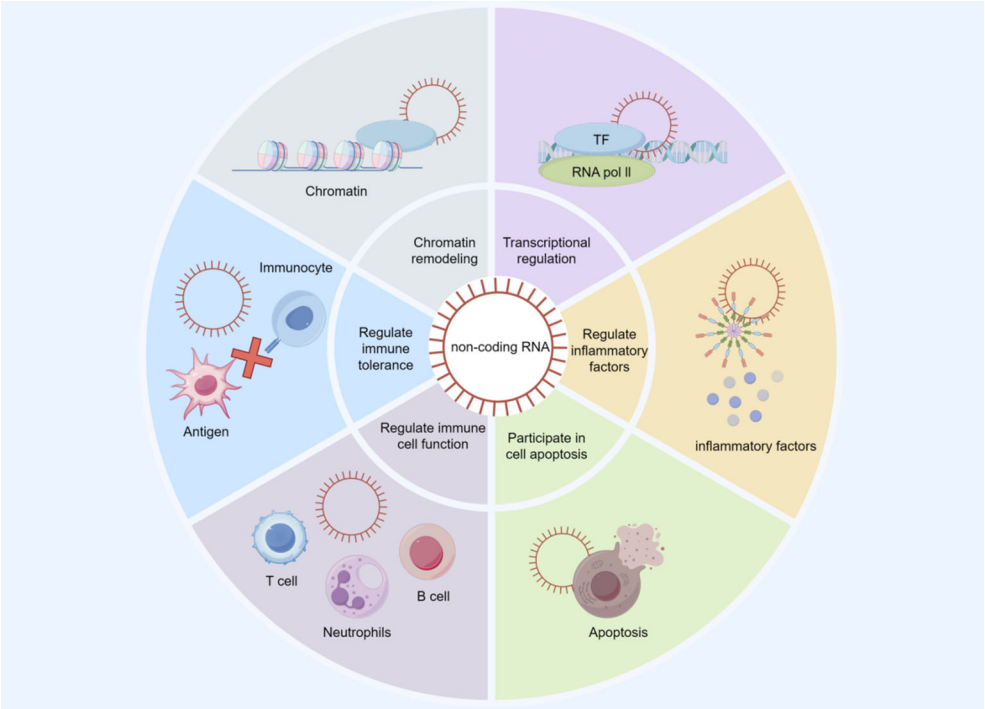

FIGURE 2
The role of non-coding RNA in the pathophysiological mechanisms of sepsis.

specificity and variability of biomarker expression across diverse populations. Notably, the study calls into question the generalizability of these findings, as variations in immune response dynamics can complicate the interpretation of such biomarkers in heterogeneous patient cohorts.

Similarly, Ge Jing et al. sought to delineate crucial biomarkers through an analysis of coagulation-related gene expression, identifying FCER1G and FYN as significant candidates through advanced machine learning techniques (135). While methods such as ROC curve analysis provided a validation framework, the reliance on computational models raises concerns about the potential for overfitting and the applicability of derived biomarkers in real-world clinical settings. Moreover, the focus on specific gene sets may obscure broader pathophysiological mechanisms operating in sepsis, suggesting a potential risk of simplification that could misdirect clinical strategies. In contrast, George et al.'s clinical case study of an atypical presentation of Lemierre's syndrome illustrated the necessity of clinical acumen over biomarker reliance, emphasizing a clear gap in biomarker knowledge when faced with unusual manifestations of infectious conditions (136). The findings corroborate the limitations of biomarker reliance, as clinical indicators alone may inadequately capture the complexity of conditions such as sepsis, thereby endorsing a multifaceted approach that integrates clinical judgment, laboratory tests, and imaging findings in achieving timely diagnoses. Expanding on management strategies, Mushtaq Ammara et al.'s systematic review elucidates advances in sepsis care yet simultaneously highlights the variability in treatment outcomes attributed to differing clinical practices (137). The findings advocate for a multidisciplinary approach while prompting scrutiny regarding the standardization of intervention protocols. Additionally, Douglas et al. underscored the positive outcomes associated with dynamic fluid resuscitation techniques within septic shock patient management (138). However, the study emphasizes the necessity for extensive clinical trials to establish the efficacy of such novel techniques over traditional practices, raising questions about the empirical validity of using biomarkers for guiding therapeutic decisions in fluid management. Lastly, Fowler et al. critically assessed established predictive scoring systems within a cohort of critically ill patients undergoing debridement procedures, revealing shortcomings in the predictive capabilities of SIRS and qSOFA scores compared to MEWS (139). This observation reinforces the potential for misclassification of risk in patient management, highlighting an essential challenge in the clinical application of biomarkers. The study elucidates the necessity for ongoing validation of these scoring systems in larger populations to ascertain their clinical utility, thereby questioning the robustness and reliability of current approaches.

In summary, while the exploration of biomarkers such as sCD137, FCER1G, and FYN presents exciting avenues for enhancing sepsis prognostication and personalized approaches to therapy, substantive limitations persist in terms of specificity, generalizability, and clinical relevance. These challenges necessitate an integrative framework that incorporates both biomarker analysis and clinical judgment, ensuring that management strategies remain responsive to the multifactorial nature of sepsis and its varied presentations. As research progresses, a concerted focus on validating and standardizing

TABLE 1 List of diagnostic sepsis biomarkers.

Biomarker	Source	Response time	Diagnostic accuracy	Clinical significance	Strengths	Limitations
CRP (39, 82–84)	Liver (induced by IL-6)	Rises within 6–12 hours after infection	Moderate (high sensitivity, low specificity)	General inflammation screening, disease monitoring	Rapid, low cost, widely available	Non-specific (elevated in non-infectious inflammation)
PCT (21, 22, 85–87)	Thyroid C-cells, periph eral tissues	Rises within 2–4 hours after infection	High (specific for bacterial sepsis)	Guides antibiotic use, predicts severity	Strong correlation with bacterial infection	False positives in trauma or surgery; higher cost
IL-6 (38–40, 88, 89)	Macrophages, T-cells, endothelial cells	Rises within 1–2 hours after infection	High sensitivity, moderate specificity	Early sepsis warning, reflects cytokine storm	Rapid response, correlates with organ failure	Short half-life; elevated in non-septic conditions
IL-10 (90–93)	Regulatory T-cells, monocytes	Rises within 3–6 hours after infection	Moderate (predicts immunosuppression)	Indicates anti-inflammatory response, poor prognosis	Reflects immune dysregulation	Non-specific; levels vary with comorbidities
TNF-α (20, 94, 95)	Macrophages, NK cells	Rises within 1–2 hours after infection	High early sensitivity, low specificity	Initiates cytokine cascade, linked to septic shock	Early marker of inflammation	Transient release; limited utility in late sepsis
CD64 (96–98)	Neutrophil surface (upregulated in sepsis)	Rises within 4–6 hours after infection	High specificity for bacterial infection	Distinguishes bacterial vs. viral infections	Improves accuracy with neutrophil count	Requires flow cytometry; limited dynamic data
sTREM-1 (99–101)	Neutrophils, macrophages	Elevates within 6–8 h after infection	Moderate (higher in bacterial sepsis)	Identifies infection-related inflammation	Good specificity in localized infections	Unstable in plasma; assay standardization issues
Presepsin (102–104)	Monocytes/ macrophages (CD14 cleavage)	Elevates within 2–3 h after infection	High (early bacterial sepsis marker)	Early diagnosis, prognosis assessment	Faster rise than PCT; correlates with severity	Limited data in non-bacterial sepsis; cost
circRNAs (105–107)	Cytoplasm/exosomes (e.g., immune cells)	Unknown (likely early)	Emerging (tissue-specific potential)	Novel markers of gene regulation in sepsis	High stability; multi-target potential	Complex detection (RNA sequencing); unvalidated
HOTTIP (78, 108, 109)	Plasma (long non-coding RNA)	Unknown	Experimental (correlates with severity)	Linked to organ dysfunction and inflammation	Epigenetic insights; prognostic potential	Mechanism unclear; lacks standardized assays
microRNA-486-5p (110, 111)	Plasma/exosomes (endothelial/immune cells)	Early (preclinical)	High potential (needs validation)	Regulates apoptosis/ inflammation; prognostic value	Stable, non-invasive; dynamic monitoring	Technical challenges (PCR/ sequencing); variability

biomarkers will be critical to improving their applicability and enhancing patient outcomes in this complex clinical landscape.

6 Integrative approaches to biomarker identification and treatment strategies

6.1 Early Recognition and Intervention Protocols

The early recognition and intervention protocols for sepsis are critical to mitigating morbidity and mortality rates, necessitating a spectrum of innovative methodologies and biomarkers for timely diagnosis and treatment. Villanueva-Congote et al. conducted a retrospective cohort study to evaluate the prognostic significance of the Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Neutrophil Ratio (PLR) in patients with obstructing ureteral stones and suspected urosepsis, revealing a notable association between elevated NLR and PLR with increased qSOFA scores, a requirement for vasopressors, and ICU admissions, which signals the potential of these metrics for early risk stratification and resource allocation in clinical practice (140). This study's utilization of logistic regression provides quantitative backing to the clinical importance of routine laboratory indices as adjuncts in early sepsis identification. Similarly, Chamani Ali et al. embarked on a protocol for a randomized controlled trial to assess the efficacy of synbiotic supplementation in critically ill septic children, targeting inflammatory markers such as interleukin-6 and C-reactive protein. With a sample population of 54 pediatric patients, this prophylactic approach leverages a combination of probiotics and prebiotics to mitigate systemic inflammation and enhance gut integrity, highlighting a promising low-cost therapeutic strategy with approachable clinical implications (141). Parallelly, You Ruilian et al. focused on earlier detection of sepsis-induced acute kidney injury (SI-AKI) by investigating kidney-specific cell-

TABLE 2 (Established/adjacent).

Biomarker(s)	Primary clinical role	Evidence level	Clinical readiness	Key caveats
Lactate (serial measurement) (17)	Risk stratification; monitor resuscitation response	Guideline-endorsed	Routine	Not specific for sepsis; interpret with perfusion signs; kinetics depend on shock type and treatment.
Procalcitonin (PCT) (17)	Adjunct to support antibiotic de-escalation/discontinuation	Guideline-suggested (weak/low)	Adjunct/ conditional	Should not be used alone to diagnose sepsis; performance varies by infection source, renal function, and timing.
C-reactive protein (CRP) (84, 112, 113)	Adjunct inflammation marker; trend monitoring	Supported by observational	Adjunct/ conditional	Low specificity; affected by many inflammatory states; trends more informative than single cutoffs.
Interleukin-6 (IL-6) (39, 89)	Severity/prognosis; may help identify hyperinflammation when interpreted with other markers	Supported by observational	Adjunct/ conditional	Assay- and cohort-dependent thresholds; rapid kinetics; best interpreted longitudinally.
Neutrophil-to-lymphocyte ratio (NLR/ PLR) (114, 115)	Low-cost risk stratification	Supported by observational (heterogeneous)	Adjunct/ conditional	Strongly confounded by comorbidities/medications; population-specific cutoffs; limited incremental value vs clinical scores.
CD64 (neutrophil CD64) (97, 98)	Adjunct diagnosis in selected settings	Supported by observational/meta-analyses	Adjunct/ conditional	Platform and cutoff variability; requires flow cytometry; turnaround time may limit ED use.
Presepsin (sCD14-ST) (116, 117)	Adjunct diagnosis/prognosis	Supported by observational/meta-analyses	Adjunct/ conditional	Renal dysfunction affects levels; assay availability varies; not universally standardized.
suPAR (118, 119)	Prognostic enrichment (severity/mortality)	Supported by observational	Adjunct/ conditional	Non-specific; elevated in many chronic/inflammatory conditions; best for risk enrichment not diagnosis.
MR-proADM (120, 121)	Prognosis; hemodynamic/organ dysfunction risk	Validated observational	Near-term adjunct	Assay availability/cost; may add incremental prognostic value but needs prospective pathway studies.

Biomarkers graded by level of evidence and clinical readiness.

free DNA (cfDNA) methylation markers through genomic sequencing. Their compelling findings demonstrated high accuracy in distinguishing SI-AKI from patients without kidney injury, evidenced by an AUC of 0.92, suggesting that cfDNA levels correlate positively with the severity of kidney injury, thus offering a transformative biomarker that could streamline patient management (142). In a further exploration of metabolic deficiencies in acute settings, Joseph Miller et al. highlighted the prevalence of thiamine deficiency among sepsis patients, estimating its occurrence at 20.5% and identifying its associations with age, gender, and leukopenia, thus advocating for routine screening and timely supplementation strategies that could potentially improve outcomes in vulnerable populations (143). Concurrently, the study by Smyth Michael A et al. leveraged machine learning alongside logistic regression analysis to identify sepsis in ward patients, achieving a predictive accuracy that could heighten diagnostic efficiency in hospital settings. The investigation underscored the importance of integrating specific vital signs and laboratory results to augment traditional diagnostic methodologies, ultimately aiming to enhance clinical response mechanisms (144). Furthermore, advances in understanding the molecular underpinnings of sepsis, such as the work by Yan Uralian et al. examining the protective effects of dexmedetomidine on sepsis-induced AKI, illuminated the modulation of oxidative stress and ferroptosis through the Keap1-Nrf2 signaling pathway, revealing potential therapeutic avenues for renal protection during sepsis (145). Likewise, Priputnevich Tatiana

TABLE 3 (Investigational).

Biomarker(s)	Primary clinical role	Evidence level	Clinical readiness	Key caveats
Endothelial/glycocalyx markers (e.g., Ang-2, syndecan-1) (122–125)	Phenotyping; vascular injury severity	Exploratory	Research	Assay heterogeneity; unclear decision thresholds; clinical actionability not established.
DAMPs/NETs (e.g., cfDNA, mtDNA) (126–128)	Pathobiology; severity association	Exploratory	Research	Preanalytical variability; limited standardization; unclear added value beyond routine labs.
Transcriptomic/gene-expression signatures (129–131)	Endotype stratification; prognostic enrichment	Exploratory	Research	Requires external validation across settings; platform/ turnaround time constraints; prospective impact unknown.
Metabolomic/multi-omic panels (132–134)	Discovery phenotyping; risk models	Exploratory	Research	High complexity/cost; reproducibility and standardization challenges; needs pragmatic workflows.
Mechanistic targets from omics (e.g., macrophage-associated genes) (30)	Hypothesis generation; therapeutic target discovery	Exploratory	Research	Primarily experimental evidence; requires clinical validation and interventional studies.

Biomarkers graded by level of evidence and clinical readiness.

V et al. underscored the continued need for vigilant monitoring in neonatal sepsis by evidencing the association of *Malassezia furfur* with invasive fungal infections in vulnerable populations, thus calling for improved diagnostic protocols to identify and treat these infections swiftly in very low birth weight infants (146). Collectively, these studies reflect an emerging consensus on the necessity of integrating advanced biological markers, innovative therapeutic interventions, and machine learning analytics into early detection and treatment frameworks for sepsis, underscoring their potential to significantly improve clinical outcomes and foster research into pathogen-specific and patient-centric care strategies.

6.2 Detection strategies for sepsis identification

Recent advancements in sepsis detection strategies have progressively embraced innovative methodologies and technologies, demonstrating significant potential to enhance diagnostic accuracy and timeliness. The study by de Oliveira Veloso Rezende Jéssica et al. delineated a pioneering dataset to facilitate pathogen detection, integrating differential cell lysis and mass spectrometry-based proteomics from whole blood samples. This multifaceted dataset encompasses Spectral Libraries, spiked pathogen mass spectrometry data for biomarker optimization, and Parallel Reaction Monitoring (PRM) data, achieving a remarkable sensitivity of 83.3% within a seven-hour timeframe without the need for microbial enrichment culture, thereby establishing a solid foundation for creating bioinformatics tools aimed at combating antibiotic resistance (147). Complementarily, Griffin Kitiara et al. revealed an innovative affinity-based microfluidic chip that significantly streamlined the clinical detection of sepsis by capturing specific immune cells in blood samples. Notably, their analysis of 125 septic patients demonstrated substantial differences in antigen cell counts compared to controls, with an exceptional combined area under the ROC curve (AUC) of 0.997, thus highlighting the chip's diagnostic accuracy and potential to enhance patient outcomes through rapid intervention (148). Furthermore, the exploration of machine learning frameworks for sepsis prognostication, particularly by Rahman Md Sohanur et al. showcased the efficacy of utilizing a Stacking-based Meta-Classifier on a sizable cohort from the MIMIC-III database, achieving a notable accuracy of 95.52%. This underscores machine learning's transformative potential in real-world clinical applications, enhancing risk prediction capabilities significantly (149). Building on the same technological frontier, the work by Liu Fei et al. further substantiated the applicability of machine learning in acute pancreatitis-associated sepsis, employing LASSO regression to distill meaningful features and subsequently revealing the gradient boosting decision tree (GBDT) model's superiority with an AUC of 0.985 over traditional scoring methods (150). Moreover, the study by Li Lu et al., investigating systemic inflammatory response syndrome patients, effectively integrated neurophysiological data with clinical attributes to enhance prognostic modeling—exhibiting a robust classification congruence, thereby facilitating early interventions and rehabilitation strategies in intensive care (151).

In parallel, metagenomic next-generation sequencing (mNGS) has emerged as a formidable tool in rapidly identifying pathogens in critically ill patients, as evidenced by the research conducted by Li Chaozhong et al. The significant sensitivity of mNGS, which identified a wide array of infections in a cohort of 150 patients, illuminates its clinical relevance compared to traditional microbiological tests (152). Equally notable is the innovative framework presented by Zheng Xubin et al., dubbed scCaT, which enhances sepsis diagnosis through single-cell RNA sequencing, achieving impressive performance metrics across multiple datasets. This model not only augments classification accuracy but also enriches biological understanding by elucidating gene groupings associated with sepsis diagnosis, showcasing the power of combining deep learning with genomic data (153). Finally, Lazzarino et al. offered critical qualitative insights into the implementation of computerized clinician decision support systems (CCDSSs) in sepsis management, underscoring the necessity for aligning these tools with clinical workflows, improving alert accuracy, and considering contextual factors that influence their effectiveness (154). Overall, the convergence of advanced imaging techniques, machine learning, genomic analyses, and real-world clinical inputs demonstrates a robust trajectory towards redefining sepsis detection strategies, emphasizing the crucial role of interdisciplinary approaches in improving diagnostic and therapeutic outcomes for this formidable condition.

6.3 Biomarker application in resource-limited settings

In low- and middle-income countries (LMICs), the application of sepsis biomarkers often relies on low-cost, readily available markers. Despite the limitations in advanced diagnostic technologies, such as high-throughput sequencing and multi-omics platforms, LMICs have made significant strides in utilizing basic biomarkers for early sepsis detection and management. Biomarkers such as the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and lactate levels are particularly valuable in these settings, providing essential information for rapid triage and decision-making in critically ill patients (155).

NLR, a simple ratio of neutrophils to lymphocytes, has shown promise as a diagnostic and prognostic biomarker for sepsis. It is particularly useful in LMICs due to its low cost, ease of measurement, and ability to reflect systemic inflammation. Studies have demonstrated that elevated NLR correlates with higher mortality and severity of sepsis, making it an important tool for early risk stratification in resource-limited environments. Similarly, PLR, another easily measured inflammatory marker, has been identified as a reliable predictor of sepsis in various patient populations. Both NLR and PLR can be calculated from standard complete blood count (CBC) tests, which are widely available even in resource-constrained settings (156, 157).

Lactate, a well-established biomarker for tissue hypoperfusion, remains a cornerstone of sepsis management, particularly in LMICs. Its rapid measurement, often within an hour, enables timely intervention and risk assessment, especially in settings where advanced molecular diagnostic tools are unavailable.

Elevated lactate levels (≥4mmol/L) are consistently associated with poor outcomes and increased mortality in sepsis, making it a critical marker for early diagnosis and treatment initiation. Additionally, serial lactate measurements and lactate clearance have been shown to improve prognostic accuracy and guide therapeutic decisions, enhancing survival rates in resource-limited environments.The ANDROMEDA-SHOCK trial demonstrated that lactate clearance during resuscitation is associated with improved outcomes, but also clarified that lactate-guided resuscitation should be interpreted in conjunction with peripheral perfusion assessment (158). When combined with rapid microbiological diagnostics, lactate levels can guide clinicians in initiating appropriate therapy, ensuring timely diagnosis and treatment despite the lack of high-throughput technologies (156, 159, 160).

6.4 Advanced diagnostic techniques and technologies

The emergence of advanced diagnostic techniques and technologies has revolutionized our understanding of sepsis and its associated complications, thereby enhancing potential therapeutic strategies. Li Guilin et al. harnessed single-cell RNA sequencing to dissect the alterations in cell composition and communication among peripheral blood mononuclear cells (PBMCs) in both healthy individuals and those afflicted with sepsis and septic shock. Their meticulous investigation revealed not only a marked increase in Resistin signaling in sepsis monocytes but also a significant enhancement of IL16 signaling in septic shock, substantiated through robust flow cytometry and bulk RNA-seq analyses (161). These findings position CAP-1 and IL16 as promising diagnostic biomarkers, offering the potential to refine early diagnostic methods and tailor individualized treatment strategies. In contrast, Xie Lijun et al. explored the protective role of propofol against sepsis-induced myocardial dysfunction, employing a blend of echocardiographic assessments, histological analyses, and molecular techniques to elucidate the compound's therapeutic capacity. Their study underscores propofol's efficacy in ameliorating cardiac function and reducing oxidative stress through mTOR signaling inhibition, indicating its role as a novel therapeutic intervention for sepsis-associated cardiomyopathy (162). Concurrently, Chen Mingchao et al. presented compelling evidence linking decreases in circulating CDC42 expression to increased susceptibility, multi-organ dysfunction, and elevated mortality in sepsis patients compared to healthy controls. Employing RT-qPCR methodologies, they established CDC42 as a prognostic biomarker with a notable area under the curve (AUC) of 0.766, thereby signaling its critical role in inflammatory responses and organ dysfunction. This highlights the diagnostic potential for assessing patient risk profiles in sepsis scenarios (163). In clinical settings, the significance of rapid recognition and management of sepsis is further articulated by Bleakley et al., who emphasize the indispensable role of nursing staff in the timely application of the 'sepsis six' protocol. Their comprehensive review emphasizes the life-saving potential of early interventions and advocates for enhanced training to improve outcomes through prompt identification of septic symptoms (164). From a broader perspective, Evans et al. illuminate the complexities surrounding sepsis management, revealing the multifaceted nature of its pathogenesis, which includes endothelial dysfunction and dysregulated cardiovascular responses, further complicating the establishment of a definitive molecular signature. They argue for a unified approach involving timely antibiotic therapy and fluid resuscitation as integral components of effective sepsis management, despite the lack of targeted therapies to date (17). Khanum Iffat et al. shed light on skull base osteomyelitis (SBO) as a condition considerably impacted by sepsis, identifying significant risk factors that exacerbate morbidity among patients, thereby calling for refined diagnostic approaches in this context (165). Furthermore, the systematic analysis by Qian Hang et al. reveals noteworthy epidemiological trends regarding maternal sepsis, indicating fluctuations in incidence rates and mortality that highlight the disproportionate burden on specific demographics, such as women in the African Region. Their findings raise critical questions concerning the global disparities in managing maternal sepsis and the associated challenges (166). Lastly, the work by Chen Zhenfeng et al. provides insights into the molecular mechanisms underlying sepsis-induced acute lung injury (SALI) by illuminating the role of oligoadenylate synthetase 3 (OAS3) and its regulation through TRIM21-mediated pathways. Employing integrative multi-omics analyses, they elucidate a novel therapeutic target that could advance clinical interventions for this severe condition (167). Collectively, these studies underscore the imperative for continued innovations in diagnostic technologies and treatment strategies, fostering a multifaceted approach to tackling the challenges posed by sepsis and its various manifestations.

6.5 The role of machine learning and bioinformatics in sepsis detection

6.5.1 Experimental models

The landscape of sepsis detection has been profoundly transformed by the integration of machine learning and bioinformatics, as evidenced by recent studies that emphasize diverse methodological advancements and their implications for patient outcomes. Garcia Lopez Albert et al. focused on elucidating the risk of developing sepsis postoperatively by analyzing preoperative whole-blood RNA sequencing data from 267 patients undergoing major elective surgeries. Their application of machine learning classification models demonstrated remarkable predictive capability, achieving an area under the curve (AUC) of 0.910 in forecasting postoperative sepsis outcomes based on transcriptomic signatures (168). This not only highlights the ability of machine learning to uncover complex biological patterns associated with sepsis but also suggests a promising avenue for personalized risk stratification and management strategies. Conversely, the study by Dias Fernando Suparregui et al. addressed a fundamental obstacle in the clinical management of sepsis: the inconsistencies surrounding its definitions. By employing cohort studies and meta-analyses to evaluate the efficacy of existing criteria across a diverse dataset of clinical cases, they revealed critical discrepancies in diagnosis and

management frameworks that necessitate the refinement of sepsis definitions (169). The implications of such refinements are profound as they could promote standardization and ultimately enhance the sensitivity and specificity of sepsis detection, fostering a more robust approach to treatment strategies.

6.5.2 Clinical implementation systems

In clinical practice, the application of machine learning has moved beyond experimental models to become integrated into real-time decision-making systems. Brabrand Mikkel et al. reinforced the operational relevance of machine learning by validating the quick Sequential Organ Failure Assessment (qSOFA) score for the timely identification of septic patients in emergency contexts through a thorough retrospective analysis of patient records (170). Their findings affirm that the qSOFA score acts as an effective triage tool, which is especially crucial in high-stakes environments where time-sensitive decisions are essential for improving patient outcomes. Complementing these quantitative analyses, Machado Flavia Ribeiro et al. employed a mixed-methods approach to assess the applicability of the Sepsis-3 definition within middle-income settings, revealing both advantageous diagnostic precision and significant resource challenges posed by its implementation (171). This underscores the necessity for contextual adaptation of diagnostic criteria, indicating that successful sepsis management may hinge on the local healthcare capacity and resource availability. Furthermore, the innovative work by Lawati et al. diverges slightly from the primary focus on detection to treatment, exploring the effects of large-bore percutaneous mechanical aspiration combined with early surgical intervention for patients with refractory staphylococcal infective endocarditis complicated by sepsis (172). Their findings highlight an adjunctive therapeutic strategy that offers effective source control, thereby illustrating how adaptable clinical practices can bridge the gap when faced with complex challenges like sepsis. Collectively, these studies underscore the critical role of machine learning and bioinformatics in enhancing sepsis detection and management. They advocate for interdisciplinary approaches that incorporate statistical rigor and contextual relevance to refine diagnostic criteria and optimize treatment algorithms, ultimately striving towards an integrated healthcare model capable of meeting the multifaceted demands of sepsis management. Although numerous ML-based sepsis prediction models have been proposed, current guideline-level documents consider these tools largely investigational and do not recommend routine clinical adoption in standard sepsis workflows without robust external validation and prospective impact evaluation (55).

6.6 Innovative therapeutic approaches and pharmacological interventions

The evolving landscape of sepsis management has witnessed a noteworthy emphasis on innovative therapeutic strategies and pharmacological interventions, particularly through the exploration of diverse biomarkers and clinical decision-making tools. In a prospective controlled study, Song Juhyun et al. evaluated the diagnostic and prognostic capabilities of IL-6, pentraxin 3 (PTX3), and PCT in a cohort of 142 sepsis and septic shock patients, demonstrating the superior diagnostic potential of IL-6 compared to PTX3 and PCT, with significant correlations drawn between elevated IL-6 levels and 28-day mortality outcomes (37). This work reinforces the dependency on objective biomarkers for stratifying sepsis severity, crucial for therapy optimization in clinical settings. Similarly, the research by But Špela et al. utilized machine learning techniques alongside a comprehensive dataset of 497 neonates, successfully creating an online application designed to predict neonatal sepsis risk by identifying significant clinical markers, including C-reactive protein and procalcitonin levels (173). This predictive tool underscores the potential of integrating advanced computational methodologies into everyday clinical practice to facilitate early intervention, thus enhancing patient outcomes.

In examining potential pharmacological interventions, Wang Zheng et al. illuminated the cardioprotective effects of Po-Ge-Jiu-Xin decoction (PGJXD) in sepsis-induced cardiomyopathy via a robust animal model employing cecal ligation and puncture (CLP) methodology. Their findings indicated that PGJXD significantly mitigated mortality and myocardial injury, activating the PINK1/Parkin-mediated mitophagy pathway in the process (174). This highlights the dual role of novel herbal remedies not only as adjunct therapies but also as pathways toward understanding the biological mechanisms underlying sepsis-related complications. These experimental mechanisms provide hypotheses for future therapeutic development, although their relevance to human sepsis requires further clinical validation. In terms of cost-effectiveness, a study by Mosly Mohamed Metwally et al. aimed to juxtapose procalcitonin-guided management against conventional culture-based approaches within the Egyptian healthcare context. Utilizing a decision tree model, the analysis yielded an Incremental Cost-Effectiveness Ratio (ICER) of 297,783.57 Egyptian Pounds per QALY for procalcitonin guidance; however, it lacked cost-effectiveness dominance due to high diagnostic costs, thereby calling for economic improvement strategies surrounding PCT utilization in sepsis (175). As clinical settings grapple with budgetary constraints, the findings accentuate the necessity for economic assessments of biomedical interventions.

Moreover, Özer Abdullah et al. illuminated the predictive capacity of monocyte distribution width (MDW) for diagnosing postoperative sepsis among patients undergoing cardiovascular surgery, establishing an optimal MDW cutoff value for enhanced diagnostic accuracy (176). This reaffirms the growing practice of incorporating emerging inflammatory markers into clinical decision-making paradigms. Parallelly, research by Gomez et al. highlighted degradation of the endothelial glycocalyx as a potential indicator of critical illness outcomes in neonatal foals through longitudinal biomarker measurement, suggesting transferability of these findings into clinical veterinary practices as well (177). A bioinformatics analysis by Cao Qingfei et al. further contributed to this narrative by probing neutrophil-related genes (NRGs) associated with septic cardiomyopathy. They identified MRC1 as a hub gene through differential expression analyses, validating its potential as a therapeutic target (178). Similarly, Jacob Julie A et al. asserted that revised sepsis diagnostic guidelines centering on organ

dysfunction markedly improved early detection and treatment outcomes across a comprehensive patient database, advocating for a paradigm shift in sepsis management towards a more organ-centric approach (179). In a more specialized patient population, Mittal et al. developed a scoring system to predict outcomes in emphysematous pyelonephritis, utilizing multivariate analyses to stratify patient risk into several categories, thereby tailoring treatment modalities accordingly (180). This individualization of care exemplifies the transition towards precision medicine within sepsis treatment. Lastly, Ouyang Xiaojun et al. delineated the incidence and risk factors related to sepsis-associated acute kidney injury in pediatric patients, suggestinging actionable variables linked to poor outcomes, thereby enriching the clinical toolkit available for managing septic conditions in vulnerable populations (181).

Thus, the conglomeration of these studies epitomizes a pivotal shift toward precision-based diagnostics, innovative therapeutic interventions, and enhanced prognostic capabilities. The collective insights advocate for the integration of multidisciplinary approaches that encompass molecular biology, bioinformatics, clinical economics, and personalized medicine into the ongoing battle against sepsis, reaffirming the necessity for continuous research and development in this critical area of healthcare.

7 Future research directions

Future research in sepsis management is increasingly focusing on innovative methodologies and personalized approaches to improve patient outcomes. One promising direction is the integration of multi-omics data, which combines genomic, transcriptomic, proteomic, and metabolomic information to provide a comprehensive understanding of the biological processes underlying sepsis (182, 183). This integrative analysis can enhance the stratification of patients based on their unique biological profiles, potentially leading to tailored therapeutic interventions. Recent advancements in computational techniques, such as machine learning and hypergraph convolutional networks, facilitate the integration of multi-omics data, enabling researchers to derive meaningful insights from complex datasets. However, challenges remain in terms of data standardization, high dimensionality, and the need for robust analytical frameworks to ensure accurate interpretations (184). As the field progresses, future studies should prioritize the development of integrative multi-omics clustering methods that can effectively identify patient subgroups and suggest targeted therapies, thereby advancing precision medicine in sepsis management.

7.1 Potential of integrative multi-omics analysis

Integrative multi-omics analysis holds significant potential for elucidating the complex pathophysiological mechanisms underlying sepsis. By systematically integrating data from multiple omics domains, researchers can delineate molecular pathogenesis, identify novel candidate biomarkers, and uncover mechanistically relevant therapeutic targets. For example, integrating metabolomics with transcriptomic and proteomic data may characterize metabolic perturbations in sepsis, enabling earlier detection of disease progression and risk-stratified prognostic models (185). Emerging evidence indicates that multi-omics frameworks improve discriminatory power in early cancer detection, highlighting the translational potential of these approaches for sepsis phenotyping. Systematic integration of multi-dimensional datasets enables mechanism-centric disease characterization while prioritizing biomarker candidates for tailored therapeutic interventions (186). However, realizing the full clinical potential of multi-omics requires developing standardized analytical pipelines and rigorous validation frameworks to ensure biological interpretability and bedside applicability.

While multi-omics platforms and machine learning models offer substantial diagnostic and prognostic potential, they come with significant costs, particularly in terms of infrastructure, data analysis, and ongoing validation. In contrast, biomarkers such as procalcitonin (PCT), which have been widely validated for guiding antimicrobial stewardship, are cost-effective and readily available, offering clear cost-saving benefits. PCT-guided management has been shown to reduce antibiotic use and hospital length of stay, contributing to lower healthcare costs without compromising patient outcomes. This comparison underscores the need for a balanced approach, where the integration of cutting-edge technologies like multi-omics should be weighed against their economic feasibility, especially in resource-constrained settings.

7.2 Application of personalized medicine in sepsis management

Current limitations in sepsis management stem from uniform therapeutic algorithms that fail to account for interpatient heterogeneity in host-pathogen interactions and comorbid disease trajectories. Such non-stratified management paradigms neglect critical biological variables including immune endotype diversity, genetic susceptibility loci, and comorbidity-driven pathophysiological states (187). These limitations underscore the necessity for mechanistically informed stratification frameworks to optimize therapeutic precision. Precision medicine approaches leveraging multi-omic profiling and computational biology present transformative opportunities for endotype-specific sepsis care (188).

This paradigm employs multi-omic profiling (genomic, proteomic, metabolomic) to decode host-response signatures and pathogen virulence determinants (187). Emerging research identifies circulating microRNAs as dynamic risk stratification biomarkers, enabling time-sensitive therapeutic modulation (189). Systematic mapping of gene regulatory networks and molecular interactomes reveals therapeutically actionable nodes for personalized targeting (190). Integrative analysis of multi-omic datasets facilitates computational subphenotyping, guiding mechanism-targeted therapies with demonstrated mortality reduction in recent trials (191). Concurrently, AI-driven predictive modeling extracts clinically relevant patterns from high-dimensional biomarker matrices, enabling real-time treatment response forecasting (192). Translating these advances into practice necessitates overcoming

implementation challenges through multicenter validation studies and evidence-based implementation roadmaps.

8 Conclusion

Research into biomarkers for early sepsis diagnosis and monitoring shows promise, marking a crucial change in handling this serious condition. While incorporating inflammation factors, metabolic markers, and gene expression profiles into clinical practice has the potential to enhance early detection and support timely intervention, it is equally important to acknowledge the immediate clinical applicability of cost-effective biomarkers for rapid triage and decision-making.

This review emphasizes the complementary roles of bedside biomarkers, such as procalcitonin and soluble CD14 subtype, which are already proven to enhance early diagnosis and antibiotic stewardship, particularly in resource-limited settings. Additionally, we explore the potential of integrating advanced omics technologies for precision phenotyping, especially in complex cases where traditional biomarkers may not suffice.

In line with current needs, we propose a "Hybrid Model" for the future of sepsis management: an integrated approach that combines cost-effective bedside biomarkers with advanced omics technologies. This model ensures rapid, actionable insights from easily accessible biomarkers for initial patient assessment, while utilizing omics for more precise, personalized care in challenging cases. This hybrid strategy allows for a scalable, cost-effective, and clinically applicable approach to sepsis management, which can be tailored to diverse healthcare systems worldwide.

Moving forward, it is essential to develop combined panels of point-of-care (POC) biomarkers alongside quick microbiological diagnostics, enabling healthcare providers to make fast, informed decisions. While omics technologies offer great promise for sepsis stratification, the immediate relevance of POC diagnostics and stewardship-guided biomarkers cannot be overstated, especially in environments where timely interventions are critical. The success of this hybrid model will hinge on validating these biomarkers in clinical trials, refining them through real-world application, and ensuring their integration into scalable sepsis pathways applicable across diverse healthcare systems.

Ultimately, bridging the gap between research and clinical application requires a concerted effort to balance innovative technologies with clinically validated, cost-effective tools. By combining cutting-edge omics with accessible diagnostics, we can pave the way toward revolutionizing sepsis care, moving toward a future where early detection, personalized treatment, and improved patient outcomes are the norm.

Author contributions

XZ: Conceptualization, Writing – review & editing. HG: Writing – original draft. JZ: Writing – original draft. ML: Writing – original draft. SC: Supervision, Writing – review & editing. YL: Writing – review & editing, Supervision. LL: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

CRP	C-reactive protein
PCT	procalcitonin
IL-6	interleukin-6
nCD64	neutrophil CD64
TyG	triglyceride-glucose
COPD	chronic obstructive pulmonary disease
aHR	adjusted hazard ratios
CI	coagulation index
IL-10	interleukin-10
TNF-α	tumor necrosis factor-alpha
CARS	compensatory anti-inflammatory response syndrome
SII	systemic immune-inflammation index
CK-MB	creatine kinase isoenzyme MB
FFA	free fatty acid
SIMD	sepsis-induced myocardial dysfunction
CT	computed tomography
MRI	magnetic resonance imaging
POCUS	point-of-care ultrasound
AKI	acute kidney injury
miRNAs	microRNAs
lncRNAs	long non-coding RNAs
circRNAs	circular RNAs
HOTTIP	HOXA distal transcript antisense RNA
ALL	acute lymphoblastic leukemia
sCD137	soluble CD137
NLR	Neutrophil-to-Lymphocyte Ratio
PLR	Platelet-to-Neutrophil Ratio
SI-AKI	sepsis-induced acute kidney injury
cfDNA	cell-free DNA
PRM	Parallel Reaction Monitoring
GBDT	gradient boosting decision tree
mNGS	metagenomic next-generation sequencing
CCDSSs	computerized clinician decision support systems
PBMCs	peripheral blood mononuclear cells
SBO	skull base osteomyelitis
SALI	sepsis-induced acute lung injury
OAS3	oligoadenylate synthetase 3
qSOFA	quick Sequential Organ Failure Assessment
PTX3	pentraxin 3
PGJXD	Po-Ge-Jiu-Xin decoction
CLP	cecal ligation and puncture
ICER	Incremental Cost-Effectiveness Ratio
MDW	monocyte distribution width
NRGs	neutrophil-related genes.